A Phytoconstituent-MicroRNA Axis: Unveiling Therapeutic Potential in Insulin Resistance

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Abstract*— Diabetes mellitus (DM) remains a leading cause of global morbidity and mortality, with insulin resistance (IR) serving as a key underlying factor in its pathogenesis. IR, characterized by the diminished responsiveness of insulin-sensitive tissues, is a critical precursor to a spectrum of metabolic disorders, including type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and cardiovascular diseases. Recent research has underscored the pivotal role of microRNAs (miRNAs), small endogenous noncoding RNAs, in the regulation of mRNA stability and translation, thereby influencing the development and progression of IR and T2DM. Concurrently, phytochemicals—bioactive compounds derived from plants—have gained attention for their therapeutic potential, particularly due to their antioxidant, anti-inflammatory, and pharmacological properties. These natural compounds have been shown to modulate miRNA expression, regulate gut microbiota, and exert immunomodulatory effects, offering promising avenues for the prevention and management of IR and its miRNA complications. This review delves into the specific interactions between phytochemicals and miRNA profiles, exploring how these interactions can mitigate IR and reduce the risks associated. Furthermore, the review highlights the potential of miRNA as novel biomarkers for early diagnosis and prevention of IR, suggesting their integration into therapeutic strategies aimed at combating the global burden of diabetes. Through this exploration, the article aims to illuminate new pathways for the management and mitigation of IR, contributing to the advancement of diabetes care and the reduction of associated health risks.

***Index Terms*— Insulin Resistance, miRNA, Phytochemicals**

I. INTRODUCTION

In today's modern society, widespread adoption of sedentary lifestyles & Western dietary habits has become a major risk factor for developing type 2 diabetes mellitus (T2DM), posing an increasing threat to global health. Normally, elevated plasma glucose levels are regulated by insulin, which facilitates glucose uptake in major sites such as liver, skeletal muscle and adipose tissue. However, lack of physical inactivity & excessive nutritional intake places undue stress on pancreatic beta cells, escalating the demand for insulin secretion. This imbalance disrupts normal glucose metabolism and homeostasis, contributing to issues such as obesity, insulin resistance (IR) & ultimately the progression of T2DM.

IR is marked by decreased responsiveness of insulin-sensitive tissues to insulin, serving as a precursor to various metabolic disorder, NAFLD, T2DM and heart diseases (1). Before the onset of T2DM, hyperinsulinemia or pre-diabetic state signals an increased chance of getting the disease. In this phase, elevated plasma insulin levels temporarily keep hyperglycemia in check, concealing the underlying metabolic imbalance. However, over time, the persistent strain on beta cells to manage rising glucose levels leads to their dysfunction, ultimately resulting in the development of T2DM (2). The precise molecular pathway underlying IR still remains unsatisfactory, but is now made distinct to result from a blend of genetic and environmental predisposition (3). Moreover mi-RNA has been established to have its role in the pathophysiology of IR which belongs to the class of endogenous noncoding RNA that binds on to mRNA and destabilizes or inhibits their translation playing an important role in biological processes (4). Studies have observed alterations in mi-RNA levels in type 2 diabetes, providing evidence that these changes could serve as efficient marker for early diagnosis and prevention of insulin resistance(5). Phytochemicals are plant based natural product with significant

antioxidant potential & diverse range of pharmacological activity (6), Phytochemicals can also regulate gut microbiota, modulate gene translation, and exhibit immuno-modulatory actions, further contributing to their potential in managing type 2 diabetes mellitus. (7). Current anti-diabetic drugs can effectively control hyperglycemia, but they also come with potential adverse effects, in contrast phytochemicals offer a natural and safer approach towards managing onset of T2DM (insulin resistance) by alleviating harm caused by oxidation, scavenging free radicles, and regulating changes in gene expression(8,9).This article provides a coverage on determining role of certain phytoconstituents in preventing IR and occurrence of T2DM through the regulation of miRNAs expressions.

II. MICRORNAS (MI-RNAS) AND INSULIN RESISTANCE

miRNAs are short, untranslated RNA strands, usually consisting of 20-24 nucleotide base pairs, essential for regulating gene expression. They control genes via adhering to corresponding regions on specific messenger RNAs (mRNAs), resulting in silencing of gene either through degradation of the mRNA or by inhibiting its translation (Figure 1) (10). They are crucial for different biological functions, including cellular development, division and death. Aberrations in miRNA expression have been implicated in a wide range of pathologies, including neo-plasticity, metabolic disorder, heart diseases, and CNS disorders (11). As discussed previously, insulin resistance refers to inability of the insulin targeted tissues like liver, skeletal muscle & adipose tissues to respond to the signal produced by insulin for glucose uptake into the cells (3). Insulin-driven transport of glucose primarily occurs in skeletal muscle, so IR in muscle could have significant effects on overall body metabolism(12). Research has shown that IR in skeletal muscle to be linked with impairments in GLUT4 translocation(13). The liver offers an essential function in regulating lipid and glucose bioprocessing, hepatic IR is linked to lipid accumulation in liver tissue, which in turn contributes to systemic insulin resistance (14). Obesity is a significant end-point for developing insulin resistance, primarily due to metabolic changes occurring in adipocytes. Since expression of miRNA is specific tissue to tissue, chubbiness mediate altered expression of miRNA in adipocytes, which in turn affects gene expression related to insulin resistance. Therefore, variations in miRNA expression levels in obese individuals can serve as potential predictors for diagnosing insulin resistance (15).

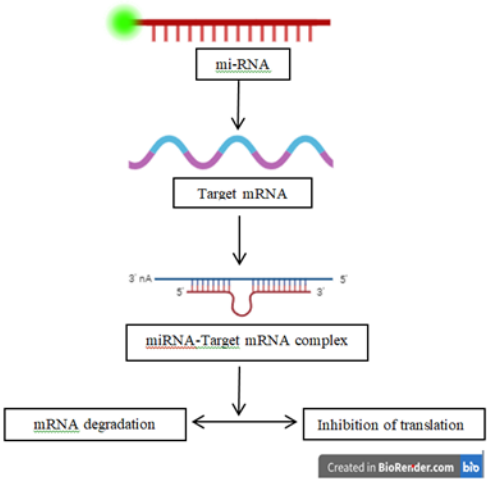

Fig 1: miRNA forms a complementary base pair with the target mRNA for inhibiting protein translation either by degrading the mRNA carrying the information about the proteins to be coded or by inhibiting the translation of the gene.

III. miRNA OF THE PANCREATIC B-CELL

miRNAs posses a important role in optimizing insulin production and development of β-cells, which are necessary for maintaining blood glucose level. Specifically, miR-9, miR-375, miR-376, and miR-7 are observed at high levels in the pancreas which have an effect in the functioning of pancreatic islets (16,17) a descriptive overview is given in Figure 2. MicroRNA-7 controls the production of the hormone glucagon-like peptide-1 (GLP-1), which triggers the release of insulin in response to elevated plasma glucose levels. It does this by blocking the action of β-arrestin 1 (βARR1), the protein typically responsible for deactivating GLP-1 receptors (18). miR-375 is mainly found in the pancreas but has several activities in the β-cell, notably helping in formation, growth, and insulin release. miR-375 hinders 3'-phosphoinositide-dependent protein kinase 1 (PDK1), and the lowered PDK1 levels contribute to a reduction in expression of the gene coding for insulin when glucose levels rise (19). The appearance of miRNA-200 subsets—which

encompasses miR-200a, miR-200b, miR-200c, miR-141, and miR-429—in islet of the pancreas governs the lifetime of β-cells and the release of insulin (5). miR-29 family, encompassing miR-29a, miR-29b-1, miR-29b-2, and miR29c, can act as essential labels for functioning of β-cell & may significantly contribute to the fundamental processes of DM and its initial stages(20).

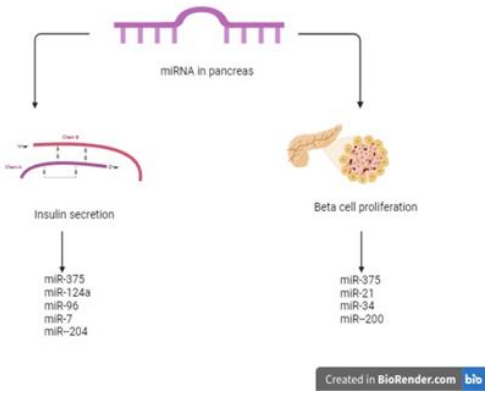

Fig 2: Different miRNA involved in insulin secretion & beta cell proliferation.

IV. LINKING MIRNA WITH INSULIN RESISTANCE

Alteration in miRNA expression has been linked with IR (Figure 3), each tissue expresses its particular miRNA such as the miR-122 i.e specific to liver hepatocytes. Insulin resistance that occurs over liver shows downfall in miR-122 levels due to over activation of c-Jun N-terminal kinase 1 (JNK1) resulting in inhibition of hepatocyte nuclear factor 4 alpha (HNF-4α) leading to hepatic IR(21). In the liver tissue FOXO1 is the major transcriptional factor for gluconeogenic enzymes transcription that promotes hepatic glucose production (5) Song et al. made a study on obese mice model where FOXO1 mRNA was increased, while hepatic miR592 was reduced which caused increase in plasma glucose levels, hepatic production of glucose and reduction in sensitivity to insulin causing IR(22) miR-9, miR-451 overexpression tends to upregulate FOXO1 expression which ultimately promotes insulin resistance whereas up-regulation of miR-146b and miR-21 tends to down regulate FOXO1 expression significantly supressing the induction of insulin resistance(23.24,25,26). Insulin resistance occurring over skeletal muscle shows increased expression of miR-17 as seen in diabetic rats also down regulation of miR-17 caused upregulation of glucose transporter (GLUT4) (27) as reduction in GLUT4 is seen in prediabetic and diabetic condition. Several miRNAs, including miR-21a-5p, miR-27a, miR-29a-3p, miR-29c-3p, miR-30d, miR-93-5p, miR-106b, miR-133a-3p, miR-133b-3p, miR-222-3p, and miR-223-3p, is recognized in regulating GLUT4 translocation (28). The imbalance of miRNAs can disrupt functions associated with fatty tissue, leading to obesity and IR(5). Representatives of the miR-29 class are closely related to decreased levels of the secreted protein acidic and rich in cysteine (SPARC), glucose transportation and GLUT4 translocation in 3T3-L1 adipose tissues (29). miR-181b, miR23a-3p, and miR-181a-5p are involved in maintaining normal glucose homeostasis and sensitivity of insulin to adipose tissue was found to be lowered in the fatty tissues of mice model of obesity (30,31). TNF-α boosts up miR-335 in fatty tissues, which reduces the activity of genes associated with insulin signaling and lipid biotransformation. This creates a connection between inflammation and metabolic dysfunction in the adipocytes. (32).

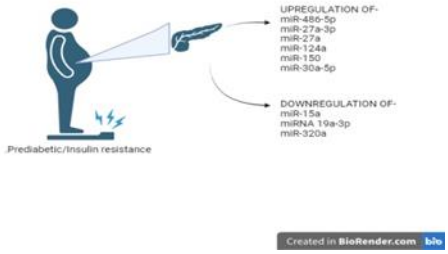

Fig 3: Diagrammatic representation of up and down regulated miRNAs in prediabetic individuals with insulin resistance.

V. CIRCULATING miRNAS AS MARKERS OF INSULIN RESISTANCE:

miRNAs that are present in living biologic fluids, specifically blood, have been utilized as non-invasive diagnostic tools for several diseases, including metabolic disorders in accordance with the findings that miRNAs represent a vital part in several pathways implicated in metabolic diseases like DM (33,34).Traditional serum biomarkers like leptin (35) and adiponectin (36) do not consistently correlate with

obesity-related complications, such as insulin resistance. miRNAs are stable in blood and play a role in regulating insulin signaling, making them potential circulating biomarkers for insulin resistance. Specific miRNAs linked with insulin resistance is spotted in obese individuals along with associated metabolic dysfunctions (36,37). A study identified elevated levels of miR-342, miR-223, miR-30d, miR-215, miR-221, and miR-122 as indicators of developing insulin resistance, even though fasting glucose, adiponectin, and leptin levels remained unchanged (38). In both human and animal model of obesity, similar changes were observed in circulating miRNAs, involving miR-122 and miR-192. These miRNAs were previously clubbed with obesity & associated disorders like IR in both humans and animal models (39,40,41). A link amongst plasma miR-210 & IR has been established (41), studies have shown increase in miR-210 to be connected alongside pancreatic β-cell mortality in mice with diabetes (42). Thus miRNAs could serve as potential biomarkers for identifying insulin resistance and monitoring the progression of beta cell dysfunction as of in T2DM though there is a distortion in the expression of specific miRNAs in pre-diabetic condition (43). miR-155 has a significance over the functioning of the beta cells, elevated levels of miR-155 signifies response to an overabundance of nutrients, adaption mediated disruption in this physiological system is a major predictor for conversion of pre-diabetic to T2DM (44). Rising concentrations of inflammatory mediators, specifically TNF-α are at the center of events linked to inflammation & IR (45). A study found that the amount of TNF-α and IL-6 was considerably greater in diabetes and pre-diabetic subjects contrasted with normal subjects. These outcomes coincided with accordance with prior studies that indicated a greater concentration of TNF-α in T2DM patients (46,47),increased expression of TNF-α and IL-6 causes IR via stimulation of the JNK and MAPK signalling mechanisms & therefore disturbs the insulin receptor cascade resulting in insulin resistance (48,49). a strong correlation amongst miRNA-122 with TNF-α and IL-6 were observed (47) discovery verifies the outcomes of prior studies demonstrating how specific miRNA-122 transcription patterns can be employed as a potent diagnostic in prognosis of T2DM & insulin resistance that is compatible with preceding researches(50,51). Attenuation of miR-125a in an in-vivo study revealed association with decreased insulin sensitivity simultaneously in an obese animal model elevated expression of miR-125a attenuated obesity-mediated insulin resistance and alteration in glucose metabolism thus indicating miR-125a to be a potential marker in diagnosis of insulin resistance that is preceded by obesity common in present era of westernized diet and sedentary life culture (52). Plasma miR-122 expression are predicted with probable establishment of metabolic disorders within the overall population (53), miR-9, miR-28-3p, miR29a, miR-103, miR-30a-5p, and miR-150 circulating concentrations when paired alongside HbA1c might additionally predict adults who are vulnerable (54). Yang et al. recommended plasma miR-23a to be a biological marker for prior identification of T2DM & pre-diabetes having adequate tolerance to glucose (55).Thus with the available data we can identify miRNAs to a potential biomarker that can be used as a diagnostic for the onset of a disease.

VI. CHALLENGES IN TAKING UP miRNA LEVELS AS POTENTIAL MARKERS IN PRE-DIABETES VS T2DM

Taking up miRNA as a biomarker in T2DM has its own disadvantage in contrast to pre-diabetic state where the miRNA levels in the later stage of T2DM shows variations (56), shift in the miRNA profile could begin or arise during the earliest or could happen as an outcome of the development of disease. A follow-up study was made in search for the quest between diabetic and pre-diabetic individuals where circulating miR-192 was elevated in case of pre-diabetes whereas no changes were observed in T2DM(57), Another similar study findings showed fall in miR-192 levels in T2DM(58) such kind of conflicting issues requires further clarification with much in depth studies. A study made on miR-155 reflected fall in levels in diabetic individuals, as gene expression of this particular miRNA impart an important function during insulin down-streaming pathway for promoting the genes associated with glucose uptake within skeletal muscles & adipocytes which demarcates the occurence of IR(44). Study conducted by Lucena et al. revealed that persons with T2DM had elevated circulating status of miR-150 and miR-30a-5p, whereas levels of miR-15a and miR-375

were declined, compared to individuals who did not develop T2DM throughout a period of 5 years. The levels of these microRNAs were intermediate in persons who acquired pre-diabetes (pre-DM) compared to those who had previously developed pre-DM (59). Thus we can conclude that using gene expression levels to identify the later stages of metabolic disorders may not be ideal due to variations as discussed above, but they can mark as a tool for detecting early onset of metabolic disorders. This awareness can help individuals understand their risk and motivate lifestyle changes to prevent disease development.

VII. PHYTOCHEMICALS INVOLVED IN MODULATING MICRO-RNA EXPRESSION AND THEIR IMPACT ON INSULIN RESISTANCE

miRNAs could serve as biomarkers for insulin resistance, with their expression potentially being modulated in response to various therapeutic intervention & strategies(60). Recent studies indicate phytochemicals specifically polyphenols in regulating micro-RNA expression, the interactions between them remain largely unexplored. Baselga-Escudero et al. proposed that polyphenols due to their structural similarity may directly interaction with mature miRNAs, in modulating their expression (61).

Epigallocatechin gallate (EGCG) is a bioactive flavonoid molecule that contains 8 unbound -OH atoms, making it a active substance with diverse medicinal effects against hypoxic brain stroke, type 2 diabetes, insulin resistance, and heart ailments etc present abundantly in green tea (62). Drinking green tea can improve insulin resistance and sensitivity (63), based on in vitro study EGCG inhibits miRNA-33a & miRNA-122 mediated metabolic syndrome and insulin resistance (61). A pre-clinical study showed that administration of polyphenol rich green tea for a period of twelve week in obese mice model resulted in reduction of miR-335 articulation within the adipocytes. The up-regulation of miR-335 through TNF-α within fatty tissue appears to establish a connection amongst inflammation and disrupted metabolism in adipocytes(64). Human study was also carried out in high risk obese womens for insulin resistance with acute administration of green tea, and was observed for changes in circulating miRNAs which resulted in inhibition of expression of 62 miRNAs mediated by a consumption of a fatty meal (65).

Isorhamnetin (IHN) (3′-O-methyl quercetin) in an diabetic animal model promoted the appearance of AKT2 mRNA, miR-1, and miR-3163 in both muscle and adipocytes which are known in contributing to the emergence of IR, autophagy & T2DM as correlated with report made by Abdelmageed et al. that AKT2 was downregulated in diabetic models which are involved in glucose transportation, migration of fatty acid, glycogen synthase activity, and IR (66) also Li-Fang et al. discussed under expression of miR-1 during IR (67) which were all well optimized by Isoharmnetin administration. Combinational study between EGCG and IHN showed protection towards β cells via inhibiting overexpression of miR-16-5p (68) also regulated expression of miR-27a-3p and miR-96–5p by alternating FOXO1 and modulating IR(69).

Resveratrol another bioflavonoid sourced from grapes, dark chocolate, peanuts etc. (70) is believed to have numerous effect on molecular signalling and genetic regulation including epigenetic regulation (71) thus this epigenetic regulating potential of resveratrol do offer a therapeutic approach towards regulating miRNA mediated insulin resistance. Based on randomized, double-blind, placebo-controlled study co-administrarion of resveratrol promoted miRNA-126 expression which was associated with decline in apoptotic rate of beta cells and optimizing insulin secretion (72,73) miRNA-21 is demonstrated to alleviate oxidative damage in pancreatic cells by diminishing the generation of H_2O_2 mediated free radicles. This protective mechanism is facilitated through the administration of resveratrol, which also modulates the glycolytic pathway (71). Resveratrol improved insulin resistance in a rodent model of IR brought on by a fatty diet via upregulating the expression of mmu-miR-363-3p, which in turn triggered the signaling cascade that involves protein kinase B (AKT) and phosphatidylinositol 3-kinase (PI3K). (74). Still there is a need for a depth in study for fully understanding the implication of resveratrol in epigenetic regulation.

Curcumin, a polyphenol found in turmeric (*Curcuma longa*), is recognized for its diverse pharmacological properties. However, its therapeutic use is limited due to its low solubility in aqueous solutions, coupled with poor metabolism and bioavailability (75). Not much of studies have been reported in regulating circulating miRNA levels with curcumin, in a fructose mediated insulin resistance rat model increase in miR-206 expression by curcumin was reported to alleviate insulin signalling dysfunction (76).

Hesperidin a citrus bioflavonoid present in citrus fruits such as orange and lemon is a potent antioxidant phytoconstituent with therapeutic resolutions to a diverse range of disorders or illness (77). miR-149 is believed to be a significant regulator of both IR and mitochondrial impairment in the muscles of skeletal system(78) Ruan et al. had demonstrated protection offered by miR-149 to beta cells against reactive oxygen species and high glucose mediated apoptosis of beta cells (79) also miRNA is linked with mitochondrial dysfunction in skeletal muscle through inhibition of PARP-2 thus in a cell line study of high glucose -induced oxidative injury, alteration of mitochondrial function & IR LO2 cells, hesperidin as predicted down regulated the overexpression of miR-149 playing a beneficial role in diabetes (80). A human trial involved the intake of orange juice alongside an isocaloric beverage and a diet rich in calories & fat, with plasma glucose levels and micro RNAs measured at baseline and at specific time period post-consumption. The study revealed that consuming the HFHC meal with orange juice led to pronounced impression of circulating miR-375, the miRNA of pancreatic islets. miR-375, known for its functioning in regulating insulin release and maintaining glucose equilibrium, is recognized as an independent predictor of the functioning of β- cells in the pancreas, contributing to the prevention of hyperglycemia (81).

Ellagic acid, a polyphenol naturally present in plant extracts, fruits, and nut demonstrates multiple pharmacological features, like antihyperglycemic, antiinflammatory, antioxidant, and hepatoprotective actions research has indicated ellagic acid is capable of stimulating miR223, and could work as an indicator of cellular oxidative damage. Moreover, it affects kelch-like ECH-associated protein 1 (keap1), an essential modulator of oxidative response and carbohydrate processing, suppressing its transcription in HepG2 cells challenged to concentrated levels of glucose (82).Thus based upon the extracted information from various sources insulin resistance and the progression of beta cell dysfunction can be regulated in correlation to various miRNA levels indicating the therapeutic potential of various phytochemical in management, prevention & initiation of insulin resistance. Additional research is needed to confirm and understand how phytochemicals work to prevent or alleviate metabolic disorders and its complications by influencing miRNA expressions.

CONCLUSION

MicroRNAs (miRNAs) are essential in cellular proliferation, protection, transformation, and genetic regulation. Research indicates that non-coding RNAs, including miRNAs, could serve as pharmacological targets due to their involvement in various cellular processes. miRNAs impart a vital act in insulin production, β-cell action, and glucose utilization, influencing IR and T2DM. Furthermore, miRNAs may be used as innovative biomarkers to identify and treat metabolic syndrome, their association with the disease may not establish causality demanding further clinical studies to validate these findings. Modulating epigenetic expression represents a new strategy for defining and developing therapeutic approaches in diabetology. Identifying new biomolecules linked to the genetic predisposition of diseases remains unexplored, offering significant opportunities for therapeutic innovation. IR continues to be a multifactorial interaction of environmental, genetic, and physiological factors, necessitating more in-depth research. To evaluate the safety and effectiveness of phytochemicals and their combinations in clinical trials, extensive research is required. With their ability to affect the expression of non-coding RNA, including a range of foods high in phytochemicals that are plant-based in the diet may prove advantageous in the long run.

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